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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/765,287	09/12/97	LOCHT C	960-25

HM12/0926

NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON VA 22201

EXAMINER	
DEVI,S	
ART UNIT	**PAPER NUMBER**
1645	21

DATE MAILED: 09/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/765,287	Locht et al.
Examiner	**Group Art Unit**
S. Devi, Ph.D.	1645

☒ Responsive to communication(s) filed on *06/16/2000.*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-22, 27-30, and 34-39* is/are pending in the application.

Of the above, claim(s) *36 and 37* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-22, 27-30, 34, 35, 38, and 39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Change of Art Unit Location

1) Effective 20 June 2000, the Art Unit location of the instant application in the US PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1645.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 06/16/00 (paper no. 20) in response to the non-final Office Action mailed 03/16/00 (paper no. 19).

Status of Claims

3) Claim 1 has been amended via the amendment filed 06/16/00 (paper no. 20).

Claim 31 has been canceled via the amendment filed 06/16/00 (paper no. 20).

New claim 39 has been added via the amendment filed 06/16/00 (paper no. 20).

Claims 1-22, 27-30 and 34-39 are pending.

Claims 1-22, 27-30, 34, 35, 38 and 39 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

6) The objection to the drawings under 37 CFR 1.84 or 1.152 for the reasons stated on PTO 948 (attachment to paper n. 14) is maintained for reasons set forth therein.

Objection(s) Moot

7) The objection to claim 31 made under 37 CFR 1.75(c) made on page 4 of the Office Action mailed 3/16/2000 (paper no. 19) as being improperly dependent, is moot is light of

Applicants' cancellation of claim 31.

Rejection(s) Moot

8) The rejection of claim 30 made on pages 5 and 6 of the Office Action mailed 3/16/2000 (paper no. 19) under 35 U.S.C. § 103(a) as being unpatentable over Loosmore *et al.* (EP 453216) in view of Menozzi *et al.* (*FEMS Microbiol. Lett.* 78: 59-64, 1991) is moot in light of Applicants' cancellation of the claim.

Rejection(s) Maintained

9) The rejection of claims 16 and 17 made on page 4 of the Office Action mailed 3/16/2000 (paper no. 19) under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and those that are set forth here below.

Applicants contend that claims 16 and 17 refer to cultures that belong to the species *E. coli* or to a bacterial species other than *Bordetella* transformed by a recombinant DNA comprising a sequence of the invention. Applicants admit that claim 1 recites introducing the sequence into a *B. pertussis* cell culture and expressing it in the *B. pertussis* culture, but state that this does not mean that the sequence cannot be introduced into a bacterium other than *Bordetella*. Applicants refer to some prior art publications which state that *Fha* can be expressed in bacterial species other than *Bordetella* as long as *fhaC* gene is also expressed in such cells.

The Applicants' arguments have been carefully considered, but are not persuasive. The issue here is not whether or not *fhaC* gene can be expressed in bacterial cells other than that of *Bordetella*. Claims 16 and 17 are not independent claims, but depend indirectly from claim 1. Claim 1, as drafted now, requires introduction of the claimed recombinant DNA into a *B. pertussis* cell culture followed by its expression in *B. pertussis* cell culture. However, claims 16 and 17, in addition to encompassing the limitations of claim 1, recite prokaryotic bacteria other than *B. pertussis* including *E. coli*, thus making these claims confusing.

10) The rejection of claims 1-22 and 27-30 made on pages 5 and 6 of the Office Action mailed 3/16/2000 (paper no. 19) under 35 U.S.C. § 103(a) as being unpatentable over Loosmore *et al.* (EP 453216) in view of Menozzi *et al.* (*FEMS Microbiol. Lett.* 78: 59-64, 1991) is maintained for reasons set forth therein and those that are set forth here below. New claim 39, which replaces old claim 31, is now included in this rejection. See paragraph 13 below.

Applicants contend that instant invention relates to recombinant DNAs encoding fusion proteins comprising a Fha portion fused to a polypeptide that is heterologous with respect to Fha and that the fusion is performed so that an effective immune response can be raised against the heterologous antigen. Applicants contend that Loosemore *et al.* is different from the claimed invention in that the fusion in Loosemore's disclosure is only made between a promoter and a coding sequence. Applicants further assert that the fused sequences "both come from *B. pertussis*, and none of the constructs taught by Loosemore et al comprises a sequence coding for a polypeptide heterologous with respect to *Bordetella pertussis*". Applicants further argue that the promoter substitution in Loosemore *et al.* is merely performed in order to increase or decrease the yield of antigens produced in *B. pertussis* and that this can result in an improved immune response against *B. pertussis* antigens. Applicants further state that there is nothing in Loosemore *et al.* that would have led the skilled artisan to construct fusion proteins comprising a Fha moiety fused to a polypeptide heterologous with respect to Fha.

The Applicants' arguments have been carefully considered, but are not persuasive. Contrary to Applicants' arguments and statement, as drafted currently, the base claim recites that the polypeptide be heterologous to a "filamentous hemagglutinin of *Bordetella*", and does not recite that the polypeptide is heterologous to *B. pertussis*. The polypeptide expressed by Loosmore's pertussis structural gene qualifies as a "polypeptide heterologous with respect to a filamentous hemagglutinin of *Bordetella*". Whether or not Loosemore's promoter substitution is performed in order to increase or decrease the yield of antigens produced in *B. pertussis* is not relevant since instant claims are drawn to a product and not to a method of increasing or decreasing the yield of antigens produced in *B. pertussis*. With regard to the Applicants' statement that the fusion in their invention is performed such that an effective immune response can be raised against the heterologous protein, the base claim for example, recites "fusion proteins", as opposed to "the heterologous antigen", being highly immunogenic. Therefore, the reference of Loorsemore *et al.* is properly applied under 35 U.S.C. § 103(a).

With regard to the reference of Menozzi *et al.*, Applicants acknowledge that the reference teaches the Fha-heparin interactions, but contend that it does not teach a fusion protein construct comprising a Fha moiety.

The Applicants' argument has been carefully considered, but is not persuasive. The reference of Menozzi *et al.* has been applied to indicate the art-known fact that the Fha, for example of Loosemore *et al.*, contains the heparin interaction site. That the hybrid gene of Loosemore *et al.* expresses Fha that contains the heparin interaction site is implicit in the disclosure of Loosemore *et al.* in light of what is well known in the art, as taught by Menozzi *et al.* The reference of Menozzi *et al.* is proper art under 35 U.S.C § 103(a).

11) The rejection of claims 34, 35 and 37 made on pages 6 and 7 of the Office Action mailed 3/16/2000 (paper no. 19) under 35 U.S.C. § 103(a) as being unpatentable over Loosmore *et al.* (EP 453216) in view of Menozzi *et al.* (*FEMS Microbiol. Lett.* 78: 59-64, 1991) and Locht *et al.* (*Mol. Microbiol.* 9: 653-660, 1993) is maintained for reasons set forth therein and those that are set forth here below.

Applicants acknowledge that Locht *et al.* teach the immunogenic properties of Fha, but contend that Locht *et al.* do not suggest that fusion proteins comprising a Fha moiety would exhibit immunogenic properties specific for the heterologous polypeptides.

The Applicants' argument has been carefully considered, but is not persuasive. The reference of Locht *et al.* teaches the immunogenicity of FHA when presented to the mucosal immune system. Given this disclosure, it would have been obvious to one of ordinary skill in the art at the time the invention was made to present Loosemore's composition as modified by Menozzi *et al.* to the mucosal immune system to produce the instant invention, with a reasonable expectation of success, absent evidence to the contrary. As set forth on page 7 of the Office Action mailed 03/16/2000, one skilled in the art would have been motivated to produce the instant invention in order to achieve efficacious and long-lasting local or mucosal immunity as taught by Locht *et al.*

New Rejection(s)

12) Applicants are asked to note the new rejection made in this Office Action. The Applicants' amendment, i.e., the addition of a new claim, necessitated the new ground(s) of rejection presented in this Office Action.

Rejection(s) under 35 U.S.C. § 103(a)

13) Claim 39 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Loosmore *et al.*

(EP 453216) in view of Menozzi *et al.* (*FEMS Microbiol. Lett.* 78: 59-64, 1991). See paragraph 10 above for reasons of rejection.

Prior Art

14) The prior art made of record is not relied upon currently in any rejection, but is considered pertinent to Applicants' disclosure:

- Relman *et al.* (US 6,036,960) disclose a *Bordetella pertussis* cell or strain expressing a fusion protein or hybrid protein comprising a part of the filamentous haemagglutinin or FHA and a part of a protein heterologous to FHA, and a method of producing such a cell (see claims and column 9, last paragraph). The host organisms or strains that may be used can be from other pathogens. The various host organisms may be *Bordetella pertussis*, *Bordetella avium*, *Bordetella bronchiseptica*, *Bordetella parapertussis, E. coli, Salmonella, Yersinia or Pseudomonas* (see column 4, lines 44-48). Strain BP-Tox6 produces FHA and Fim2 (see Table 3 and column 7, lines 19-22). The use of the strains in prophylaxis (i.e., as vaccines) and therapy of pertussis or whooping cough and in conditions where "immune response to more than one antigen is desired", is disclosed (see column 29, lines 32-46 and column 2, lines 16-22). The strains are used as vaccines contained in pharmaceutically compatible exeipients, such as, water, saline, phosphate buffered saline and the like, and may provide an immune response not only to the subject proteins or portions thereof, but also to other pathogens resulting in immune protection, not only against *Bordetella pertussis*, but also against disease caused by other pathogens (see column 4, lines 33-44 and column 6, lines 35-58). The stimulation of murine polyclonal response by fhaB fusion proteins indicates that FHA contains numerous immunogenic domains (see column 10, lines 26-32).

Remarks

15) Claims 1-22, 27-30, 34, 35, 37 and 39 stand rejected.

16) **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

18) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 a.m. to 4.00 p.m. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
S. Devi
Patent Examiner
September 2000

L. F. Smith
LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600